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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,693	02/02/2001	Mike A. Clark	PHOE-0060	9010

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,693	CLARK ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,27 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 6-7, 27, 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **10/22/04** has been entered.

Accordingly, claims 1-2, 6-7, 27, 31-36 are examined in the instant application.

The following are the remaining rejections.

REJECTION UNDER 35 USC 103

Rejection under 35 USC 103 of claims 1-2, 6-7, 27, 31-36 pertaining to being obvious over US 5,804,183 in view of Takaku, H et al, 1995, Jpn. J Cancer Res, 86: 840-846, IDS# AM, in paper No:6, on 06/19/01, Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01 , and Oyanagi, K et al, 1986, Tohoku J Exp Med (Japan), 148 (4): 385-91, remains for reasons already of record in paper of 08/30/04.

Applicant argues that FILPULA (US 5,804,183) teaches a method for treating cancer or carcinoma or melanoma in a mammal, comprising administering arginine deaminase (AD), wherein the cancer is deficient in argininosuccinate synthetase (ASS).

Applicant argues that FILPULA does not teach a method for identifying a cancer susceptible to AD therapy, by detecting the presence or absence of argininosuccinate synthetase (ASS).

Applicant argues that Sugimura looked at ASS expression using RT-PCR, i.e. evaluating ASS mRNA and not protein expression. Applicant argues that in the Office action of January 02, 2003, the Office stated that ASS RNA could not be predictably correlated to translation into protein, and the Office is now taking exactly the opposite position. Applicant argues that the previously submitted Declaration of Mike A Clark states that histochemical detection of argininosuccinate synthetase protein (ASS) is an effective means for determining the incidence of ASS deficiency in human tumors, and that these features are taught by Applicants, and not by the cited references.

Applicant's arguments in paper of 10/22/04 have been considered but are found not to be persuasive for the following reasons:

FILPULA (US 5,804,183) teaches a method for treating cancer or carcinoma or melanoma in a mammal, comprising administering arginine deaminase (AD) to reduce the level of argine in said mammal, wherein the cancer is deficient in argininosuccinate synthetase (ASS).

Although FILPULA (US 5,804,183) does not teach a method for identifying a cancer susceptible to AD therapy, by detecting the presence or absence of argininosuccinate synthetase (ASS), however, in view of a clear correlation between the low level of arginosuccinate synthetase (ASS) gene expression in human melanoma cell lines and high sensitivity to AD, based on the teaching of Sugimura et al, and in

view that not all tumor cells are susceptible to arginine deprivation (AD) therapy, and further in view that cancers such as carcinoma, melanoma or hepatoma that have been successfully treated by arginine deprivation (AD) therapy, as taught by US 5,804,183, Takaku et al, all are deficient in or have reduced level of ASS, as taught by US 5,804,183, Takaku et al, and Oyanagi et al, it would have been obvious to identify cancer patients susceptible to arginine deprivation (AD) therapy, comprising detecting the presence or absence of ASS protein in a cancerous tumor sample.

Further, Sugimura et al teach that low mRNA level of ASS gene expression is found in several human melanoma cell lines which exhibit high sensitivity to AD treatment, and that this correlation between low level of ASS gene expression and sensitivity applies as well to normal cells, such as human peripheral blood lymphocytes.

Based on the absence of ASS mRNAs in several of the melanoma cell lines taught by Sugimura et al, one would have expected that more likely than not the encoded ASS protein would also be absent in these cell lines. Further, one would have expected that similar to the mRNA ASS level, the ASS protein level in the melanoma cell lines would be absent or low, because the supply of arginine is depleted in these melanoma cell lines treated with AD. It is noted that AD action is catalyzing arginine to citrulline, thus depleting the supply of arginine, which normally is synthesized or supplied from citrulline by the enzyme ASS, if the enzyme is present, as taught by Takaku et al. Further, the deficiency of ASS protein level in the melanoma cell lines would reflect the in vivo conditions, where melanoma patients deficient in ASS are successfully treated with AD, as taught by US 5,804,183 (FILPULA).

Further, it is noted that the rejection of January 02, 2003, the Office stating that ASS RNA could not be predictably correlated to translation into protein has been withdrawn after review and reconsideration, and thus is not applied in the present 103 rejection.

Applicant argues that TAKAKU merely suggests that an increased in level of citrulline or ammonia is not the direct mechanism of growth inhibition by AD. Applicant argues that decreased level of arginine in TAKUKA study is a result of AD therapy, which depletes arginine and interrupts the polyamine biosynthesis pathway. Applicant argues that TAKAKU does not teach or suggest anything regarding prediction based on enzymatic deficiency, much less ASS protein deficiency. Applicant concludes that thus TAKUKA does not make up for the deficiencies of FILPULA in view of SUGIMURA.

The Examiner takes noted that Takaku et al was recited to show that AD has been successfully used for in vivo treating of mice implanted with four kinds of tumor cell lines, hepatoma, colon carcinoma, sarcoma and melanoma (p.840, first column, lines 5-11 of second paragraph), and that the mechanism of growth inhibition of AD is due to depletion of essential nutrient L-arginine, and blocking the polyamine biosynthesis pathway, and not to the production of ammonia or L-citrulline (abstract, and page 843, second column, under tumor cell growth mechanism of a-AD, bridging page 844).

Applicant argues that the Oyanagi reference fails to teach or suggest that cancers such as carcinoma, melanoma, or hepatoma are deficient in, or have reduced levels of argininosuccinate synthetase. Applicant argues that the reference fails to teach

or suggest that any type of cancer cell, much less carcinoma, melanoma, or hepatoma, is deficient in, or has reduced levels of, argininosuccinate synthetase.

The arguments are not found to be persuasive. Oyanagi et al teach that a patient, patient 2, who died of hepatoma, has citrullinemia, a disease caused by deficiency of argininosuccinate synthetase in liver tissue (abstract, and page 385, last paragraph, bridging page 386). Thus hepatoma seems to be associated with citrullinemia, a disease caused by deficiency of argininosuccinate synthetase in liver tissue, in view of the teaching of Oyanagi et al.

Applicant argues that Applicant is the first to demonstrate that tumor cells that are sensitive to arginine deiminase exhibit sensitivity because the cells lack argininosuccinate synthethase. Applicant argues that the remaining possibilities, lack of argininosuccinate lyase or citrulline transporter molecules, were not excluded prior to Applicant's efforts.

This is not found to be persuasive. Contrary to Applicant arguments, Applicant is not the first to demonstrate that tumor cells that are sensitive to AD treatment exhibit sensivity to AD because the cells lack ASS. Sugimura et al clearly demonstrate a correlation between the low level of ASS expression and high sensitivity to AD treatment, supra.

Concerning Applicant's arguments that the remaining possibilities, lack of arginosuccinate lyase or citrulline transporter molecules were not excluded prior to Applicant's efforts, it is noted this does not exclude the fact that the low level of ASS is correlated to high sensitivity of AD treatment, as taught by Sugimura et al, and thus the

obviousness of identifying cancer patients having a decrease of or deficient in ASS for treating with AD, similar to the cancer patients deficient in ASS that are treated with AD in US 5,804,183.

In summary, in view of a clear correlation between the low level of arginosuccinate synthetase (ASS) gene expression in human melanoma cell lines and high sensitivity to AD, based on the teaching of Sugimura et al, and in view that not all tumor cells are susceptible to arginine deprivation (AD) therapy, and further in view that cancers such as carcinoma, melanoma or hepatoma that have been successfully treated by arginine deprivation (AD) therapy, as taught by US 5,804,183, Takaku et al, all are deficient in or have reduced level of ASS, as taught by US 5,804,183, Takaku et al, and Oyanagi et al, it would have been obvious to identify cancer patients susceptible to arginine deprivation (AD) therapy, comprising detecting the presence or absence of ASS protein in a cancerous tumor sample.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

January 03, 2005